DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Rec'd 8/18/08

Docket No. FDA–2007–N–0475

Dear Midodrine Application Holder:

Please refer to our letter dated August 7, 2007, seeking input on a number of legal/regulatory questions regarding the availability and potential scope of 3-year exclusivity for new clinical studies if holders of approved midodrine hydrochloride applications were to complete collaboratively or individually the required post-marketing studies to verify the clinical benefit for midodrine hydrochloride.[1]

Midodrine hydrochloride was approved under the Agency's accelerated approval regulations in 21 CFR part 314, subpart H on September 6, 1996. The NDA approval was based on a surrogate endpoint with the requirement that the sponsor complete phase 4 studies to verify the efficacy of midodrine in improving symptoms of patients with orthostatic hypotension as a condition of approval. To date, no application or supplement containing phase 4 studies that verify the clinical benefit of midodrine hydrochloride has been approved. If an application or supplement containing studies that verify clinical benefit for midodrine hydrochloride is not approved soon, we will issue a Notice of Opportunity for a Hearing on the Center's proposal to withdraw the approval of the midodrine hydrochloride new drug application (NDA) (and all ANDAs referencing that NDA) pursuant to 21 CFR 314.530.

We have received responses to the questions posed in our August 7, 2007 letter and we have the following comments:

Under the Federal Food, Drug and Cosmetic Act at 21 U.S.C. 355(c)(3)(E)(iii) and (iv) and 21 U.S.C. 355(j)(5)(F)(iii) and (iv) and applicable FDA regulations, a sponsor (including the NDA sponsor or the sponsor of an approved ANDA) may be eligible for 3-year exclusivity for a new clinical study if it submits a 505(b)(1) or 505(b)(2) NDA or supplemental NDA that meets the following criteria:

1. the application contains "reports of new clinical investigations (other than bioavailability studies),"
2. the new clinical investigations are "essential to approval" of the application, and
3. the new clinical investigations were "conducted or sponsored by" the applicant.

Thus, if you submit an application or supplement containing new clinical studies other than bioavailability studies that you have conducted or sponsored and those studies verify the clinical benefit of midodrine hydrochloride and are essential to the approval of labeling changes for that drug, you will be eligible for 3-year exclusivity for new clinical studies for those labeling changes. Under the statute, this will prevent FDA from approving a subsequent ANDA or 505(b)(2) application or supplement for the same conditions of approval until the 3-year exclusivity period has expired. You will be considered to have conducted or sponsored the investigations for purposes of 3-year exclusivity if you demonstrate that you or your predecessor in interest provided "substantial support" for those investigations. Pursuant to FDA regulations at 21 C.F.R. 314.108(a), to demonstrate "substantial support" you must provide a certified public accountant's statement that you provided "50 percent or more of the cost of conducting

[1] These issues were originally assigned docket number 2007N-0311. The number was changed to FDA-2007-N-0475 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

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the study or an explanation why FDA should consider [you] to have conducted or sponsored the study if [your] financial contribution is less than 50 percent or [you] did not sponsor the investigational new drug." At its discretion, a sponsor who has obtained 3-year exclusivity may waive that exclusivity to permit approval of one or more applications that would otherwise be blocked by that exclusivity at any time during the exclusivity period.

We remind you that exclusivity determinations are generally made by FDA after approval of an application or supplement, based on our findings regarding the nature and sponsorship of the investigations and the specific labeling changes approved.

Sincerely,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
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/s/

Gary Buehler
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Norman Stockbridge
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